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10/731,973	12/09/2003	Eric R. First	17637 (BOT)	6433

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EXAMINER	
TONGUE, LAKIA J	

ART UNIT	PAPER NUMBER
1645	

DATE MAILED: 09/03/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/731,973	FIRST, ERIC R.	
	Examiner	Art Unit	
	Lakia J Tongue	1645	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-11* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-11* is/are rejected.

7)☒ Claim(s) *7* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Claims 1-11 are under examination and are pending.

Information Disclosure Statement

The information disclosure statement filed December 09, 2003 has been considered.

Application 10/194,805 is an improperly cited document. The application is not a published patent nor is it a pre-grant publication. Additionally, the articles that are crossed out on the IDS are not present. Thus, the above application as well as the articles that are crossed out will not be considered.

Specification

1. The disclosure is objected to because of the following informalities: within the specification one cannot find a "brief description " of the drawings. Examples of some unclear, inexact or verbose terms used in the specification are: the word "felling" in example 1 should read "feeling" (page 37, line 9). After "suggesting inflammation" there should be a period not a comma followed by a period (page 38, line 27). On this same page there are grammatical errors (example 4, line 27). There appears to be a closed bracket parenthesis missing within the first paragraph on page 39 (lines 4-11). The specification has not been checked to the extent necessary to determine the presence of all possible minor errors. Applicants cooperation is requested in correcting any errors of which applicant may become aware in the specification.

Appropriate correction required

Claim Objections

2. Claim 7 is objected to because of the following informalities: the word "form" in claim 7 should read "from". Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

3. Claims 1-11 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Claims 1-11 are drawn to a method for treating a skin disorder, the method comprising a step of administering a Botulinum toxin to a location of a skin disorder of a patient, thereby treating the skin disorder. While the toxin to be administered topically or subcutaneously can be any of the seven serotypes it is serotype A that is preferred in an amount between about 1 and 3,000 units. The method should reduce a pain or a size of the skin disorder. The skin disorders consist of a wart, corn, callus and bunion.

On page 29, lines 8-11 it is states "Thus, my invention includes use of a Botulinum toxin to treat a skin growth by causing it to regress (become smaller) and/or relieve the pain and inflammation that can accompany a skin disorder, such as a bunion, callus, neuroma, ulcer, warts, corn, or hammertoe".

The following examples will exhibit patients who were purportedly treated with Botulinum toxin:

In example 1 a 61-year-old diabetic female presents with a pain that has developed at the bottom of her heel and it has gotten worse. The patient is diagnosed with a painful bone spur at the center of the left heel. Botulinum toxin type A as 30 units total can be applied following use of a topical anesthetic, 10U/site in three subcutaneous injection sites spaces evenly apart over the painful area. On the follow up 2 weeks later the patient can report significant relief of pain and can tolerate walking. Four weeks later the patient can reported no pain and be able to tolerate walking greater distances than two weeks earlier.

What does applicant mean when they say the patient "*can* report significant relief of pain and *can* tolerate walking"? What does applicant mean when they say the patient *can* reported no pain and be able to tolerate walking greater distances than two weeks earlier? What does it mean when applicant says Botulinum toxin type A as 30 units total *can* be applied following use of a topical anesthetic? Did applicant apply the 30 units of Botulinum toxin type A? What were the results? Were the results effective?

In example 2 a 54-year-old male who has been walking extensively at a large amusement park for three days with his grandchildren, reports significant

pain on the proximal right side of his great toe, and on the plantar side of the foot pad on the same foot. The patient has had a history of painful corns and bunions on both feet, which are recurrent, despite medical and orthotic treatment. Upon examination, a 6-cm2 growth consistent with a corn and a 8 cm^2 circular, inflamed area on the plantar side, consistent with a bunion is noted. A treatment with a Botulinum toxin type A can be commenced as 50U of toxin injected (2 sites/25U each) intradermally into the corn and 30U into the bunion. 14 days later, the patient can report significant relief in both affected areas. Two months later, the patient can report a reduction of over 50% in the size of the corn and 60% of the size of the bunion, with no pain. The patient can be able to return to normal walking activities and can also tolerate walking great distances.

Was the treatment of the Botulinum toxin commenced? Did applicant inject 50U of toxin into the corn? What were the results? Were the results effective?

In example 3 a 48-year-old female presents with a history of genital warts. Examination of the patient reveals six flesh-colored bumps or tiny, cauliflower-like maculopapular warts of various sizes (0.05 cm^2 to 2 cm^2). A Botulinum toxin type A is applied directly into the wart areas via intra-dermal injection, in an effective amount of, but not limited to 5U/ cm^2, or a total of 30U. Upon follow up 4 weeks later, 3 of the smaller warts, can have disappeared completely and at 2 months, the patient can report disappearance of the remaining warts.

The sentence "A Botulinum toxin type A is applied..." (page 38, line 15) uses the present tense (is). What were the results? What is an effective

amount? The example states the warts could have disappeared, did the warts disappear?

Lastly, in example 4 a 54-year-old male has a history of painful plantar warts and returns to the clinic following an exacerbation of wart growth on the planter 25 region of his right foot. Patient has tried in bleomycin but relief was minimal and caused significant pain following injection. Therefore, a Botulinum neurotoxin is considered as an alternative and 5U/ cm^2 can be applied in a topical formulation directly to the wart for a total of 45U. On follow up 2 months later, the patient can report complete relief of pain and upon examination, there were no signs of inflammation (rubor rings not present), and 2 of the 3 warts had disappeared completely.

How many times was the alternate drug (bleomycin)? Were the results of example 4 due to the administration of the Botulinum toxin or the bleomycin? Did applicant follow up with the patient since example 4 states the patient can report complete relief of pain?

What are the factors to be weighed and considered on page 39, line 8? What does "enter appear systemically with no significant side effects" mean (page 39, line 10)?

The examples state that a Botulinum toxin can be applied and that the patients can arrive at effective results, but it is unclear as to whether the patient was treated and whether or not the results were effective. The specification continuously recites what the patient can do and the results the patients can reach, however, they are merely possibilities that appear to not have been

accomplished. There has been no positive data to suggest that the warts, corns, bunions or calluses were reduced nor has the specification shown that the applicant can treat a neuroma or the like.

As Clostridial toxins are among the most toxic substances known to man and have caused blurred vision, dry mouth, constipation, dizziness, abdominal cramps, nausea/vomiting, general weakness, apathetic behavior, orthostatic hypotension, impaired micturition/sexual function (Jenzer et al, 1975, reference submitted in US-PTO 1449,table shown on page 151), muscle paralysis (US Pat. 5,562,907, col. 1, lines 35-37), complications due to apparent diffusion of the toxin from the infected muscle(s) to adjacent muscles resulting in difficulty in swallowing, stomach feeding, resulting in paralysis (see Pat. 5,562,907, col. 5, lines 38-65 and col. 6, lines 1-14) and toxin leakage induced edema, serum albumin decrease and injury to vascular endothelium (see col. 8, lines 45-65), the local administration of any amount of a Clostridial toxin to any local location of a patient, would not serve to treat any skin disorder.

Claims 1-3, 5 and 11 recite the administration of any amount of any Botulinum toxin to a patient. The person of skill in the art would be required to carry out undue experimentation to utilize any amount of Botulinum toxin administered to any location of any skin disorder in order to obtain a desired positive therapeutic effect, especially in light of the fact that Clostridial toxins are known to evidence extensive negative side effects and even death of mammals if the amount of toxin is too high.

Binder (EP0845267 A1) discloses the potency is expressed as a multiple of the LD50 value for a reference mammal, usually a mouse. Where a mouse is the reference mammal, one "unit" of toxin is the amount of toxin that kills 50% of a group of mice that were disease-free prior to inoculation with the toxin. For example, commercially available Botulinum toxin A typically has potency such that one nanogram contains about 40 mouse units. The potency in humans of the Botulinum toxin A product supplied by Allergan, Inc. under the registered trademark "BOTOX" is believed to be about LD50=2,730 units.

Assuming a potency which is substantially equivalent to LD50=2,730 units, the neurotoxin can be administered in a dose of up to about 1000 units, although individual dosages of about 5-15 units are preferred while dosages of as low as about 2 to 5 units will have therapeutic efficacy and are particularly preferred for initial treatments and treatments where the neurotoxin is applied to more than one lesion or area at a time (Binder, EP0845267 A1).

While claims 4 and 6-10 recite a range of dosage amounts; it is not clear the therapeutically effective amount relative to a particular toxin. This application has not disclosed a therapeutically effective, non-toxic amount of a toxin that will provide a therapeutically effective treatment without harmful side effects. Additionally, it is taught that administration of more than about 500 units of Botulinum toxin A can result in an undesired systemic effect (Naumann, US 2004/0001865 A1, page 7, section 0079), therefore claims 4 and 6-10 which recites a dosage amount of between about 1unit to 3,000 units could result in a negative, not treating, effect for a skin disorder. It is not clear if the claimed range

was used. There is no recitation as to whether 1 unit or 3,000 units of Botulinum toxin A was used.

While claim 5 defines the site of administration to be topical or subcutaneous administration to a location of a skin disorder of a patient, the amount administered is not so claimed as to enable the patient to evidence a therapeutic effect, without negative side effects; the amount administered is not required to be a therapeutically effective amount, and large amounts of Botulinum toxin could result in death of a patient.

The Clostridial toxin molecule is fully toxic to any specific tissues to which it comes in contact, thus the genus of methods now claimed is not enabled for the full scope in light of the fact that any amount of toxin administered would not serve to treat a skin disorder and would not specifically inhibit the pain associated with the skin disorder when toxic effects could result in only negative side effect.

Factors to be considered in determining whether a disclosure would require undue experimentation have been reiterated by the Court of Appeals in In re Wands, 8 USPQ2d 1400 at 1404 (CRFC1988). The Wands factors to be considered are:

a. the quantity of experimentation necessary,

b. the amount of direction or guidance presented,

c. the presence or absence of working examples;

d. the nature of the invention;

e. the state of the prior art;

f. the relative skill of those in the art;

g. the predictability or unpredictability of the art;

h. breadth of the claims.

The presence or absence of working examples utilizing the administration of Botulinum toxins to a skin disorder are exemplified in the instant specification, however it is not clear that results were obtained as suggested. The quantity of experimentation necessary would be undue for the utilization of any amount of Clostridial toxin administered to any site of a patient with the broadly claimed disease, the site being the hand, foot or face- a body part in the vicinity (definition provided by the instant specification under the term "local administration" (page 21, line 5)) of a dermal or subdermal location of a patient. The specification lacks guidance with respect to the utilization of 1 unit of a Botulinum toxin or 3,000 units of a Botulinum toxin administered to any site on the patient. The amount of direction or guidance presented is minimum in terms of working examples. The results of the putative treatment regimens exemplified in the examples are unclear. Additionally, the amount of direction or guidance presented for utilization of dosage amounts in the claimed methods is not disclosed to be within a nontoxic range, the negative side effects could be deleterious to a patient, and not result in treatment of a skin disorder. The nature of the invention involves treatment of any skin disorder with any Botulinum toxin, and without any specific guidance to the contrary, could result in severe damage to the patient or even death. The art cites specific examples of dosage and

ranges that will provide a desired result, but administration of any amount of Botulinum toxin to any site in a dosage above 500 units would appear to be detrimental to a patient. Whether or not 3,000 units of the Botulinum toxin are used is questionable. The relative skill in the art is recognized as high, the breadth of the claims is so broad not only to include a corns, callus, bunion and wart, but also a neuroma, ulcer, hammertoe, dermatofibroma, keloid, mole, granuloma or keratose. Therefore, in view of all of the above, it is determined that it would require undue experimentation to use the invention as claimed.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

(e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

4. Claims 1-6, 7 and 9 are rejected under 35 U.S.C. 102(b) based upon a public use or sale of the invention. Claims 1-6 are anticipated by Binder (U.S. Patent 5,670,484).

Claims 1-6, 7 and 9 are drawn to a method for treating a skin disorder, the method comprising a step of administering a Botulinum toxin type A to a location of a skin disorder of a patient, thereby treating the skin disorder in an amount of between about 1 unit and about 3,000 units. The administration is either topical or subcutaneous. The skin disorder is treated by reducing a pain associated with the skin disorder.

Binder teaches in claims 1-3 of U.S. Patent 5,670,484 (1) a method for mitigating or inducing remission of a skin lesion associated with a cutaneous cell-proliferation disorder in a mammal comprising administering a therapeutically effect amount of a Botulinum toxin in a pharmaceutically safe form to the mammal by delivery of the Botulinum toxin to the site of the lesion. (2) The method according to claim 1 wherein the Botulinum toxin is administered by subcutaneous injection. (3) The method according to claim 1 wherein the Botulinum toxin is Botulinum toxin A (column 9, line 13). Binder shows that Botulinum toxin A has the ability to reduce the number, severity and/or frequency of appearance of lesions and associated discomfort experienced by the patient (column 5, line 51) (discomfort is defined as: **state of physical unease:** very mild pain or a feeling of being physically uncomfortable (Encarta® World English Dictionary [North American Edition] © & (P)2004 Microsoft Corporation. All rights reserved. Developed for Microsoft by Bloomsbury Publishing Plc.)) suffering from primary cutaneous disorders such as psoriasis and dermatitis (column 4, line 10). Binder further teaches the serotypes of Botulinum toxin B, C1, C2, D, F and G

(column 2, line 43). Additionally, Binder teaches a preferred administration of individual dosages of about 5-15 units (column 5, line 39).

5. Claims 1-6 and 10 are rejected under 35 U.S.C. 102(b) based upon a public use or sale of the invention. Claims 1-6 and 10 are anticipated by Binder (EP 0 845 267 B1).

Claims 1-6 and 10 are drawn to a method for treating a skin disorder, the method comprising a step of administering a Botulinum toxin type A to a location of a skin disorder of a patient, thereby treating the skin disorder in an amount of between about 1 unit and about 3,000 units. The administration is either topical or subcutaneous. Whereby reducing a size of the skin disorder treats the skin disorder.

Binder teaches an invention relates to the use of a neurotoxin for a medicament treating cutaneous cell-proliferate disorders. Specifically, the invention comprises the use of a therapeutically effective and pharmaceutically safe neurotoxin. The medicament will preferably be for the subdermal or sub-cutaneous administration, but may also be used for topical and transdermal routes of administration (page 3, section 0016, line 30). Binder shows the preferred neurotoxin of the invention is Botulinum toxin A (page 3, section 0018, line 38). Additionally, Binder shows the target tissue for administration of a neurotoxin according to the invention is skin. "Skin" as used on the disclosure shall refer to the tissue comprised of epidermal, dermal, subdermal and subcutaneous layers of cells (page 3, section 0019, line47). Lastly, Binder

teaches that the method of the invention can be expected to be effective in mitigating lesions (e.g., by reducing their size or incidence) (page 5,section 0035, line 27).

Since the Office does not have the facilities for examining and comparing applicants' composition with the composition of the prior art, the burden is on applicant to show a novel or unobvious difference between the claimed product and the prior art. See In re Best, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and In re Fitzgerald et al., 205 USPQ 594.

Conclusion

6. The prior art made of record and not relied upon is considered pertinent to applicant's disclosure.

Heckmann, M. et al. (Botulinum toxin type A injection in the treatment of lichen simplex: An open pilot study, American Academy of Dermatology, 2002, 46: 617-9) is drawn to a therapeutic effect of botulinum toxin A in lichen simplex.

Henely et al. (U.S. Patent 6,477,410 B1) is drawn to electrokinetic delivery of medicaments to a treatment site.

Kwon (Patent Application Publication, US2004/0087893 A1) is drawn to a system for delivering therapeutic cosmetic drugs. The system includes a patch that can deliver botox toxin to remove or reduce wrinkle formation and skin aging. The system is also useful for treating lesions or abnormal skin features, such as pimples, corns, warts, calluses, bunions, actinic keratoses and hard hyperkeratotic skin, which is often found on the face, arms, legs or feet.

Naumann, (Patent Application Publication US 2004/0001865 A1) is drawn to therapeutically effective doses of a neurotoxin.

7. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Lakia J Tongue whose telephone number is 571-272-2921. The examiner can normally be reached on Monday-Friday 7-3:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Lynette Smith can be reached on 571-272-0864. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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